Docket No.: 66221-0042
EV508827445US

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To: 23.JAN.2004 41927

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Date of mailing (day/month/year) 14 January 2004 (14.01.2004)	
Applicant's or agent's file reference P100933WO	**IMPORTANT NOTIFICATION**
International application No. PCT/GB2003/004388	International filing date (day/month/year) 10 October 2003 (10.10.2003)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 14 October 2002 (14.10.2002)
Applicant ML LABORATORIES PLC et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. (If applicable) The **letters "NR"** appearing in the right-hand column denote a **priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. (If applicable) An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a **priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
14 Octo 2002 (14.10.2002)	0223696.6	GB	12 Dece 2003 (12.12.2003)

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Docket No.: 66221-0042
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P100933WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/04388	International filing date *(day/month/year)* 10.10.2003	Priority date *(day/month/year)* 14.10.2002
International Patent Classification (IPC) or both national classification and IPC C12N9/02		
Applicant ML LABORATORIES PLC et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23.04.2004	24.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Mossier, B Telephone No. +49 89 2399-8706

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/04388

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-35 as originally filed

Claims, Numbers

1-48 received on 03.12.2004 with letter of 01.12.2004

Drawings, Sheets

1/8-8/8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/GB 03/04388

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 40 - 48

   because:

   ☒ the said international application, or the said claims Nos. 40 - 48 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/GB 03/04388

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11,15-34,36,40-48
	No:	Claims	12-14,35,37-39
Inventive step (IS)	Yes:	Claims	1-11,16-34,36,40-48
	No:	Claims	15
Industrial applicability (IA)	Yes:	Claims	1-39
	No:	Claims	

2. Citations and explanations

see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET International application No. PCT/GB 03/04388

Present application relates to a method of inducing an immune response whereby gene therapy is used to express both a toxin or prodrug converting enzyme as means of killing a targeted cell type and also a heat shock protein (hsp) or an inducer of heat shock protein expression that binds to an element in a heat shock protein promoter to enhance the subsequence immune response directed against such cells. Polynucleotide sequences, vectors, products, vaccines as well as methods of treatment using said products are claimed.

Re Item I

Basis of the report

I.1 The amendments filed with the letter dated 01.12.2004 fulfill the requirements of Article 34(2)(b) PCT.

Re Item II

Priority

II.1 The International Preliminary Examination Report has been based on an assumed valid priority for the present application. Should the priority of the present application not be valid, the P,X document cited in the Search Report would be relevant with respect to novelty and inventive step (Article 33(2) and 33(3) PCT).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1 Claims 40 - 48 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of the present claims 40 - 48 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item IV

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET International application No. PCT/GB 03/04388

Lack of unity

The International Preliminary Examining Authority (IPEA) considers that there are 4 inventions covered by the claims indicated as follows:

a) Invention 1: Claims 1 - 11, 19 - 33, 40 - 47 (all complete)and claims 35 - 39 (all partially)
Products comprising a polynucleotide sequence encoding a toxin or prodrug converting enzyme and a heat shock protein (hsp) or an inducer of heat shock protein expression that binds to an element in a heat shock protein promoter and the subject matter relating thereto.

b) Invention 2: Claims 12 - 15, 48 (all complete) and claims 35, 37 - 39 (all partially)
DNA vaccines comprising a polynucleotide sequence encoding a toxin or prodrug converting enzyme and the subject matter relating thereto.

c) Invention 3: Claim 16 (complete) and claims 18, 35 - 39 (all partially)
Products comprising a polynucleotide sequence encoding a nitroreductase and a polynucleotide encoding an immunostimulatory molecule and the subject matter relating thereto.

d) Invention 4: Claim 17 (complete) and claims 18, 35 - 39 (all partially)
Products comprising a polynucleotide sequence encoding a cytochrome P450 and a polynucleotide encoding an immunostimulatory molecule and the subject matter relating thereto.

The general inventive concept underlying the 4 above mentioned inventions can be seen as the provision of a "product" comprising a prodrug converting enzyme. However, this general concept is not novel since prodrug converting enzymes are already disclosed in the prior art (see ISR, e.g.: D2: page 3, paragraph 4; D3: page 4, lines 9 - 20). Since no other special technical feature (in the sense of Rule 13.2 PCT) can be distinguished which might link the subject matter of said claims, each of the above mentioned group of claims represents an independent invention (Rule 13.1 PCT).

Re Item V

Reasoned statement under Article 35(2) PCT with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such

statement

V.1 The following documents were taken into account:

D1: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; SHENGWU HUAXUE YU SHENGWU WULI XUEBAO May 2001 (2001-05), LI MING_FENG ET AL: "A candidate oral vaccine to Helicobacter pylori: Fusion protein of HspA and CtxB" XP002272812 Database accession no. prev200100290633

D2: WO 96/05866 A (BLANKENSTEIN THOMAS ;MAX DELBRUECK CENTRUM (DE); CAYEUX PEZZUTTO S) 29 February 1996 (1996-02-29)

D3: WO 01/64739 A (COBRA THERAPEUTICS LTD) 7 September 2001 (2001-09-07)

D4: US-A-5 830 464 (SRIVASTAVA PRAMOD K) 3 November 1998 (1998-11-03)

V.2 Novelty (Article 33(2) PCT)

V2.1 D3 discloses DNA elements and constructs for tumor-selective gene expression in tumors having a mutated beta-catenin/APC pathway. Constructs that comprise multiple repeats of TCF-binding element operably linked to a promoter allow tumor cell specific expression of a prodrug converting enzyme such as nitroreductase (or cytochrome P-450) and coupled with systemic administration of a suitable prodrug, such as CB1954 (or cyclophosphamide and paracetamol), selective killing of such tumor cells can be achieved (Abstract; page 4, lines 9 - 20; claims 1 - 3 and 24 - 26). On page 11, line 20 - page 13, line 14, D3 refers to the use of said nucleic constructs in the treatment of cancer and to different ways of administration of said constructs, in particular it refers to the direct local injection of said constructs. Hence, D3 is novelty destroying for the subject matter referred to in claim 12 and the thereon dependent claims 13, 14, 35, 37 - 39 (Article 33(2) PCT).

In addition, the IPEA raises the Applicant's attention to the fact that virus-directed enzyme-prodrug therapy and gene-directed enzyme prodrug therapy relying on the use of prodrug-converting enzymes such as nitroreductases are well known "in vivo" approaches to kill tumor cells (see ISR, e.g: Kerr et al., 1999). Hence, **product claims** such as claim 12 are not allowable under Article 33(2) PCT.

V2.2 The subject matter of claims 1 - 11, 15 - 34, 36 and 40 - 48 is considered as novel since it is not anticipated by the available prior art:

D1 discloses a fusion protein comprising the heat shock protein subunit A (HspA) and the cholera toxin subunit B (CtxB) and D1 further relates to the use of said protein as vaccine for the prevention and treatment against the infection of H.pylori (Abstract). Said cholera toxin subunit CtxB in isolation is not toxic, respectively is not working as a toxin, and is being used as an immunological adjuvant. Hence, the disclosure of D1 is not prejudicial to the novelty of the subject matter referred to in claims 1 - 11, 15 - 34, 36 and 40 - 48 . Said claims are therefore considered to fulfill the requirements of Article 33(2) PCT.

D2 relates to a live tumor vaccine comprising a gene encoding a cell surface protein with immunostimulatory activity (e.g. B7), a cytokine gene (e.g. IL-4, IL-7, GM-SCF) and a suicide gene (e.g. thymidine kinase gene). D2 does not disclose a "product" comprising a polynucleotide sequence encoding a toxin or prodrug converting enzyme and a heat shock protein (hsp) or an inducer of heat shock protein expression that binds to an element in a heat shock protein promoter. Hence, the subject-matter of claims 1 - 11, 15 - 34, 36 and 40 - 48 is not anticipated by D2. Claims 1 - 11, 15 - 34, 36 and 40 - 48 are therefore considered to be novel under Article 33(2) PCT.

The subject matter of D4 concerns compositions comprising heat shock/stress proteins such as hsp70, hsp90, gp96 alone or in combination with each other, noncovalently bound to antigenic molecules. Said compositions are used to augment the immune response to genotoxic and nongenotoxic factors, tumors and infectious agents (Abstract). D4 does not disclose or suggest products comprising polynucleotides sequences encoding a heat schock protein and a polynucleotide sequence encoding a toxin or prodrug converting enzyme, respectively a gene therapy approach that requires the administration of polynucleotides sequences encoding a heat schock proteins. The subject-matter of claims 1 - 11, 15 - 34, 36 and 40 - 48 is therefore considered to be novel under Article 33(2) PCT.

V.3 Inventive Step (Article 33(3) PCT)

V3.1 The dependent claim 15 refers to various different cytochrome P450 from humans and rodents. Said claim does not meet the requirements of Article 33(3) PCT, since different cytochrome P450 are well known in the prior art and since it would be obvious for the person skilled in the art to select one of these cytochrome P450 without the exercise of inventive skill.

V3.2 The present application discloses that killing cells by enzyme-prodrug therapy is associated with a anti-tumor immune response that can be improved by co-expression of heat schock proteins or inducers of heat schock protein expression. Since the available prior art documents do not contain any disclosure that could alone, or in combination with other cited documents suggest said anti-tumor effect, the subject-matter of claims 1 - 11, 16 - 34, 36 and 40 - 48 is considered to be inventive under Article 33(3) PCT.

V.4 Industrial Applicability (Article 33(1) and (4) PCT)

V4.1 The subject-matter of claims 1 - 39 is considered industrially applicable. Hence, it meets the requirements of Article 33(1) and (4) PCT.

Certain Observations on the International Application

*The following remarks on **Clarity and Sufficiency of Disclosure** (Article 6 and 5 PCT) are made:*

1) Claims 1, 12, 16, 17, 19, 32, 40, 42, 47 and 48 have been drafted as separate independent claims. Some of these claims appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and in respect of the terminology used for the features of that subject-matter (e.g. see claims 1, 19 and 32). The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.

2) The term "immunostimulatory molecule" used in claims 16 and 17 is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

Claims

1. A product comprising a polynucleotide sequence encoding a toxin or prodrug-converting enzyme and a polynucleotide sequence encoding a heat shock protein or an inducer of heat shock protein expression that binds to an element in a heat shock protein promoter

2. The product of claim 1 wherein the inducer of heat shock protein expression is selected from the list consisting of HSF-1, HSF-2, HSF-3, IRF-1 and IRF-2.

3. The product of either of claims 1 or 2, for use in killing cells in order to enhance an immune response.

4. The product of any of claims 1 to 3 wherein the immune response enhanced is an anti-tumour response.

5. The product of any of claims 1 to 4 wherein the polynucleotide sequence encoding a toxin or prodrug-converting enzyme capable of inducing necrotic cell death and the polynucleotide sequence encoding a heat shock protein or an inducer of heat shock protein expression are both components of single polynucleotide molecule.

6. The product of any of claims 1 to 5 wherein the toxin or prodrug-converting enzyme is a nitroreductase capable of activating the prodrug CB1954.

7. The product of any of claims 1 to 5 wherein the toxin or prodrug-converting enzyme is a cytochrome P450.

8. The product of claim 7 wherein the cytochrome P450 is selected from the list consisting of human CYP1A2, human CYP2E1, human CYP3A4, rodent CYP1A2, rodent CYP2E1 and rodent CYP3A4.

9. The product of any of claims 1 to 8 wherein the heat shock protein is selected from the list consisting of Hsp70, Hsp90, Hsp110, calreticulin, gp96, grp170, Hsp27, Hsc70,

Mycobacterium Hsp65, *Legionella pneumophila* Hsp60, *Escherichia coli* GroEL and GroES.

10. The product of claim 9 wherein the heat shock protein is Hsp70.

11. A DNA vaccine comprising the product of any of claims 1 to 10.

12. A DNA vaccine comprising a polynucleotide encoding a toxin or prodrug-converting enzyme for killing cells in order to enhance an anti-tumour immune response.

13. The DNA vaccine of claim 12 wherein the toxin or prodrug-converting enzyme is a nitroreductase capable of activating the prodrug CB1954.

14. The DNA vaccine of claim 13 wherein the toxin or prodrug-converting enzyme is a cytochrome P450.

15. The DNA vaccine of claim 14 wherein the cytochrome P450 is selected from the list consisting of human CYP1A2, human CYP2E1, human CYP3A4, rodent CYP1A2, rodent CYP2E1 and rodent CYP3A4

16. A product comprising a polynucleotide encoding a nitroreductase capable of activating the prodrug CB1954 and a polynucleotide encoding an immunostimulatory molecule, for use in killing cells in order to enhance an anti-tumour immune response.

17. A product comprising a polynucleotide encoding a cytochrome P450 and a polynucleotide encoding an immunostimulatory molecule, for use in killing cells in order to enhance an anti-tumour immune response.

18. The product of either of claims 16 or 17 wherein the immunostimulatory molecule is selected from the list consisting of GM-CSF, IL-1, IL-2, IL-4, IL-6, IL-10, IL-12, IL-18, B7-2, TNFα, γ-IFN, MCP-1, MIP-2, RANTES, TGF-β, CD154, CD134 ligand, MHC Class I, MHC Class II, CD135 ligand and TRAIL.

19. A vector encoding and allowing expression of
    a) a toxin or prodrug-converting enzyme and
    b) a heat shock protein or inducer of heat shock protein expression that binds to an element in a heat shock protein promoter,

    for use in enhancing an immune response.

20. The vector of claim 19 wherein the immune response is an anti-tumour response.

21. The vector of either of claims 19 or 20 wherein the heat shock protein is selected from the list consisting of Hsp70, Hsp90, Hsp110, calreticulin, gp96, grp170, Hsp27, Hsc70, *Mycobacterium* Hsp65, *Legionella pneumophila* Hsp60, *Escherichia coli* GroEL and GroES.

22. The vector of claim 21 wherein the heat shock protein is hsp70.

23. The vector of any of claims 19 to 22 wherein the toxin or prodrug-converting enzyme is a nitroreductase capable of activating the prodrug CB1954.

24. The vector of any of claims 19 to 22 wherein the toxin or prodrug-converting enzyme is a cytochrome P450.

25. The vector of claim 24 wherein the cytochrome P450 is selected from the list consisting of human CYP1A2, human CYP2E1, human CYP3A4, rodent CYP1A2, rodent CYP2E1 and rodent CYP3A4.

26. The vector of any of claims 19 to 25 wherein one or both of the polynucleotide sequences encoding of the toxin or prodrug-converting enzyme on the one hand, and the heat shock protein or inducer of heat shock protein expression on the other, operably linked to one or more promoters providing tumour-selective expression.

27. The vector of claim 26 wherein the promoter comprises one or more TCF-responsive elements.

28. The vector of any of claims 19 to 27 wherein the vector is a viral vector.

29. The vector of claim 28 wherein the vector is an adenoviral vector.

30. The vector of claim 28 wherein the vector is a retroviral vector.

31. The vector of claim 30 wherein the vector is a lentiviral vector.

32. An adenoviral vector encoding and allowing expression of
a) a nitroreductase capable of activating the prodrug CB1954 and
b) hsp70
for use in enhancing an anti-tumour immune response.

33. A host cell comprising the vector of any of claims 19 to 32.

34. A vaccine comprising the product of any of claims 1 to 10, or 16 to 18, the vector of any of claims 19 to 32, or the host cell of claim 33.

35. The product of any of claims 1 to 10, or 16 to 18, the DNA vaccine of any of claims 11 to 15, the vector of any of claims 19 to 32, or the host cell of claim 33 for use as a medicament.

36. The product of any of claims 1 to 10, or 16 to 18, the vector of any of claims 19 to 32, or the host cell of claim 33 for use as a vaccine.

37. A pharmaceutical composition comprising composition of any of claims 1 to 10, or 16 to 18, the DNA vaccine of any of claims 11 to 15, the vector of any of claims 19 to 32, or the host cell of claim 33 together with a pharmaceutically-acceptable diluent, buffer, adjuvant or excipient.

38. Use of the product of any of claims 1 to 10, or 16 to 18, the DNA vaccine of any of claims 11 to 15, the vector of any of claims 19 to 32, or the host cell of claim 33 for the manufacture of a medicament for the treatment of cancer.

39. Use of the product of any of claims 1 to 10, or 16 to 18, the DNA vaccine of any of claims 11 to 15, the vector of any of claims 19 to 32, or the host cell of claim 33 for the manufacture of a vaccine for the treatment of cancer.

40. A method of killing cells in order to enhance an immune response, comprising administering a therapeutic amount of a product comprising a polynucleotide encoding a toxin or prodrug-converting enzyme and a polynucleotide encoding a heat shock protein or an inducer of heat shock protein expression.

41. The method of claim 40, wherein the immune response is an anti-tumour immune response.

42. A method of treating a human suffering from a form of cancer, comprising administering a therapeutic amount of a product comprising a polynucleotide encoding a toxin or prodrug-converting enzyme and a polynucleotide encoding a heat shock protein or an inducer of heat shock protein expression.

43. The method of any of claims 40 to 42, comprising
a) administering a therapeutic amount of a product comprising a polynucleotide encoding a nitroreductase capable of activating the prodrug CB1954 and a polynucleotide encoding a heat shock protein,
b) allowing a period of time during which the product enters tumour cells and the encoded nitroreductase and heat shock protein are expressed, and
c) administering a therapeutic amount of CB1954.

44. The method of any of claims 40 to 42, comprising
a) administering a therapeutic amount of a product comprising a polynucleotide encoding a cytochrome P450 and a polynucleotide encoding a heat shock protein,
b) allowing a period of time during which the product enters tumour cells and the encoded cytochrome P450 and heat shock protein are expressed, and
c) administering a therapeutic amount of a prodrug.

45. The method of claim 44 wherein the prodrug is acetaminophen

46. The method of any of claims 40 to 45 wherein the heat shock protein is Hsp70.

47. A method of treating a human suffering from a form of cancer, comprising administering a therapeutic amount of a product comprising a polynucleotide encoding a heat shock protein, and a therapeutic amount of anti-cancer cytotoxic drug, such that a therapeutic anti-tumour immune response is induced.

48. A method of eliciting an anti-tumour immune response comprising

a) administering a therapeutic amount of a product comprising a polynucleotide encoding a nitroreductase capable of activating the prodrug CB1954,

b) allowing a period of time during which the composition enters tumour cells and the encoded nitroreductase is expressed, and

c) administering a therapeutic amount of CB1954.